Michael Miller, our virologist at Gilead Sciences, address that question.

DR. MILLER: Michael Miller Gilead Sciences. Can I have Slide 336, please.

[Slide.]

So, basically, in answer to your question, the exact number of baseline nucleoside-associated mutations was around 3.5, and I don't have the distribution of the actual baseline number, but I have the distribution, which you can kind of infer from looking at the distribution here of patients with no TAMs, or one or two TAMs, or three TAMs, or greater than and equal to four TAMs, and you can get a feeling from those n's in parentheses there where the n, the average was around 3 to 3.5, in that region, you get the mean or the median, and there was no appreciable difference between the active and placebo arms.

The specific types of mutations, can I have Slide 616, please.

[Slide.]

Try 516.

[Slide.]

Just in terms of the definitions that we employed, these were the resistance collaborative

group definitions, and the specific nucleoside-associated mutations are listed here. There were 16 of them. The ones in yellow are the ones that are thymidine analogue mutations according to our protocol. So, these are the mutations that we were actually counting in the analyses, as well as for the primary NNRTI and the PIs, as well.

DR. JOHNSON: Could I ask two more questions while you are up there? Could you just for information tell us what method of genotyping was used and where it was done?

DR. MILLER: Yes. In Study 907, we used exclusively Virco Laboratories for both the genotypic and phenotypic analyses, and their genotyping then goes out to amino acid 400, and that is population based analyses.

In Study 902, we used Virco for the phenotypic data, but we used Visible Genetics for the genotypic data, and they have a more limited amplimer going out to amino acid 250 for all of those patients.

DR. JOHNSON: And do you know at each of those two laboratories, were phylogenetic sequence analyses for quality assurance, that each of these

sequences was distinct from each patient analyzed at baseline or over time?

DR. MUNK: We did do quality control throughout the process. This was a blinded analysis in terms of treatment, but it was not blinded in terms of patient I.D.'s, and since we had follow-up samples from all patients, any discrepancies which were noted were then pursued to determine whether or not there was an error in the sequence analysis or not, and all of those were kind of feted out and metted out, and confirmed.

DR. JOHNSON: Finally, with regard to phenotyping, in the Study 907, there is a comment that only 85 phenotypes were presumably amplifiable out of 137 baseline samples. Was this reflecting that these were specimens, their sensitivity, 1,000 copies from, because these patients were entering the study with a lower viral load?

DR. MILLER: Yes, exactly.

DR. JOHNSON: And have you ever looked at the virologic assay in parallel with the Virco assay in any of your phenotypic analyses?

DR. MILLER: No, we have never done that head to head comparison. I think both of the companies are improving their assays, but indeed,

from studying 907, the attrition between the value of 85 and the intended value of 137 was done was due to low viral loads.

We sent them actually every sample, and they tried, and the failure rate between 50 and 1,000 was very high.

DR. JOHNSON: Was that with the older form of the Virco assay or the new and improved, do you know?

DR. MILLER: That was with the older form. I don't believe they have actually rolled out for commercial purposes the new form.

DR. JOHNSON: Thank you.

DR. GULICK: Just to let the committee know, I am going to call on people who haven't had the chance to ask questions, and then I will come back to people for additional questions.

Dr. Sun and then Dr. Yogev.

DR. SUN: Just a couple questions. One is technical, methodologic. In your in vitro studies that are cell based, such as virology and some of the safety pharmacology work, are you using tenofovir or tenofovir DF?

DR. TOOLE: DF.

DR. SUN: Is that consistent across in

vitro studies, because of the increased permeability?

DR. TOOLE: We do see approximately 100-fold increase in the potency of tenofovir when we go from comparing tenofovir to tenofovir DF, presumably because we are getting more drug in the cells.

DR. SUN: A second question relates to 907. I think one of your prespecified stratifications was on number of antiretroviral drugs at baseline. I think it is 4 or fewer and greater than 4.

Do you have that analysis because I didn't see that in the briefing package?

DR. TOOLE: That analysis was done by the FDA. That was not one of our prospectively defined subgroup analyses in Study 907.

DR. SUN: But you stratified on that basis, right?

DR. TOOLE: No, we stratified on the basis of HIV RNA less than or greater than 5,000 or CD4 counts less than or greater than 350.

DR. SUN: I am looking at page 31 of the briefing document where it says patients were stratified to viral load, as you say, CD greater or

less than 200 and number of ART drugs prior to study entry.

DR. TOOLE: I will have to go and check the protocol because it is my understanding that was not part of this. There were two stratifications.

DR. GULICK: Dr. Yogev.

DR. YOGEV: In Study 907, how many patients were more than 5,000 viral load, and how many of them were less than 400 at week 24?

DR. TOOLE: In Study 907, for the numbers of patients that had baseline viral loads greater than 5,000, was 99 in the treatment group, and I believe it was 43 in the active group. The percentage of patients that had viral loads less than 400 copies/mL at week 24 was 45 percent in the tenofovir arm and 13 percent in the placebo arm.

DR. YOGEV: That is the number you give for the whole group. Is it the same for greater than 5,000? I am asking specifically for greater than 5,000.

DR. TOOLE: I don't have that. I am sure it is less, but I don't have the exact numbers. It is important to point out, though, that this was an intensification study, and patients who had greater

than 5,000 copies/mL, in order for them to reach the less than 400 copies/mL, you are asking for a 1 log change, and there was, I think offhand, there was probably around 10 to 20 percent of patients who had a 1 log change, so I am sure it is less than the overall group, but again, it is the difficulty of achieving that, the addition of one drug to a stable background regimen.

DR. YOGEV: The main reason why I am asking is when you are asking for naive patient, not too many of us will start in less than 5,000 therapy, I am sure you are familiar, and then your recommendation is 55,000, so one would like to see how it would work there.

Also, I noticed that in your submission, you find a synergy between this drug and AZT and amprenavir. How many of the patients in your studies were on those drugs as the backbone versus other drugs, which you didn't find synergy in vitro, did you compare between those?

DR. TOOLE: No, we didn't do that analysis, but a large number of patients were also receiving AZT concomitantly, very few were receiving amprenavir.

DR. YOGEV: I noticed in 907, if you did

it, CD4, less than 200 patients, did very well against the placebo, but comparatively to those who had more than 200, didn't do that well.

Did you have any analysis, is that minus 4, minus 6, and 5, is there a statistically significant difference between the two?

DR. TOOLE: Yes, that difference is highly statistically significant.

DR. YOGEV: Not with the placebo, between themselves.

DR. TOOLE: We didn't do that comparison, however, it is important to point out that the FDA has recently conducted an analysis and discovered that part of that reason that we see less response in various subgroups has to do with baseline TAM expression, which is a confounding variable, and we have only discovered recently that the TAMs can diminish treatment response with tenofovir.

DR. YOGEV: So, would you suggest in those who have less than 200, have more TAM resistance?

DR. TOOLE: Correct.

DR. YOGEV: Can we have some analysis of with and without TAM, less than 200, because it is a population that is unique, and the response is the lowest that you have, so it would be

interesting to see if that is really the reason, which might be, or the other just affecting it, because one thing which impressed me is the CD4 response is not as one would expect to see.

The last question, in the pediatric population, your age will be from what to what?

DR. TOOLE: Our Phase III study will be conducted in children age 6 months to 17 years.

DR. YOGEV: Six months to 17 years.

DR. TOOLE: Yes.

DR. YOGEV: And you are going to subgrade them, and it will be less than 2 years, above 2 years--

DR. TOOLE: That protocol is still under development, but we will plan something like that.

DR. YOGEV: For the FDA, the safety summary, you pulled out the diarrhea and the rest, is there more of them in tenofovir by percentage, is that statistically significant?

DR. STRUBLE: Only for vomiting, and that is all grades, Grade 1 through Grade 4.

DR. GULICK: Dr. Wood.

DR. WOOD: I had a question regarding the safety analysis about bone changes specifically. Was the substudy analysis done in women? Between

902 and 907, there are only 96 females in this study.

My concern is about differences that may occur in terms of risk for changes in bone mineral density based on sex. Was that kind of analysis done?

DR. TOOLE: No, that was not done. Again, there were only 74 patients in the bone mineral density substudy in Studies 902 and 907. We expect to be able to do that in Study 903, where we will have all 600 patients being followed serially for BMD changes.

DR. WOOD: Another question regarding HIV RNA results according to demographic baseline and characteristic, and maybe somebody from the FDA might address this question, but there were several significant treatment interactions that were documented.

The most important were that there was lower response to tenofovir with greater than 5,000 copies/mL, and also with greater than 4 drugs.

What I wanted to know, is there any way those two factors can be combined and examined in an analysis together, so that we would know what the response would be for someone who had greater

than 5,000 copies/mL and had greater than 4 antiretroviral drugs in terms of past antiretroviral treatment?

DR. STRUBLE: We could look at that, but what we found is that subsequently to sending out the background, we did some other analysis looking at baseline viral load and prior antiretroviral use, and the baseline genotype, and found that those interactions went away, that they were no longer significant, that it was the presence of key mutations, specifically the 41 and 210, that affected response, and not necessarily the baseline viral load.

DR. WOOD: This is a virology question. I am not sure whether or not it was both in 902 or 907, but there was a report of the K65R genotypic mutation in six patients, but then there was also a report of a greater than 4-fold phenotypic resistance in nine patients, and I am just curious as to what the explanation is of the virologist for the phenotypic resistance in two tenofovir in the setting of a lack of a genotypic mutation.

DR. TOOLE: There were six patients whose HIV expressed a K65R mutation at baseline. Importantly, not all of those patients had more

than a 4-fold increase in susceptibility or decrease in susceptibility to tenofovir. It is generally in the range of 3- to 4-fold. So, not all those would be necessarily included when we looked at the 4-fold increase in baseline tenofovir susceptibility.

DR. SCHAPIRO: Could we see the ones, the genotypes of that, the patients you are alluding to?

DR. TOOLE: I will let Dr. Michael Miller address that question.

DR. MILLER: I don't have a specific slide showing the individual genotypes. That actually was in our study report. However, what we found is a high fraction, almost all of the patients, in fact, had both the 41L and 210W TAM. A couple of patients have the K65R, and we also had one patient who had the 269 insertion mutation, but the overwhelming dominance of greater than 4-fold reduced susceptibility appears to be due to the presence of substantial numbers of thymidine analogue mutations inclusive of 41 and 210.

DR. GULICK: I would like to give the opportunity for any committee members who haven't had the chance to ask

questions.

Dr. DeGruttola.

DR. DeGRUTTOLA: I have two quick questions. For the patients who went below 50 or below levels of detection for the calculation of the DAVG, did you just use the level of detection as the value for calculation of the primary endpoints?

DR. TOOLE: We used 50. We used the ultrasensitive assays, 50 was used for the lower limit.

DR. DeGRUTTOLA: I had a question about actually in the report, there is a Table 419 that gives responses by baseline resistance mutations in Study 907, and you break out the response for tenofovir versus placebo for some of the TAMs and some combinations like the 215 and 184, but not for others like the 210 and 41, so I was just curious how it was chosen, which categories to break out in that table, which TAMs to show the effects separately or combinations of those.

DR. TOOLE: This is the FDA's table?

DR. DeGRUTTOLA: This is Table 419 from the Gilead report on page 51.

DR. TOOLE: Okay. I will let Dr. Miller

again address that question.

DR. MILLER: Perhaps we can have Slide 87. I believe this is the one you are referring to.

[Slide.]

Basically, we have protocol-specified mutations, which we were to analyze, and then there were exploratory analyses done, so the presentations and all of the tables that were in the Gilead of background information were from the protocol-specified genotypic groupings, and these included the presence or the absence of the M184V mutation, the presence of absence of the thymidine analogue mutations, as well as, on the next slide, the presence or absence of the 215Y mutation.

[Slide.]

The other one, 69L74V and K65R, we included. They were listed in the protocol as being exploratory because we knew that they would be unlikely to be a large number of patients in those groups. Then, the additional exploratory analyses that came subsequent to that specifically looked at the patterns of thymidine analogue mutations, breaking out those six mutations specifically.

DR. DeGRUTTOLA: I see. So, then, 210 and

41 weren't mentioned in the protocol, but you found out subsequently in the exploratory analysis.

DR. MILLER: Exactly.

DR. DeGRUTTOLA: Thank you.

DR. GULICK: Dr. Dorsky.

DR. DORSKY: I had a number of questions related to safety. Were there any subgroup analyses of patients who might be heavy alcohol consumers or have had chronic diarrhea or other conditions which might predispose to phosphate wasting?

DR. TOOLE: No, we did not do any subgroup analyses looking at that.

DR. GULICK: Before I turn to going back to people, I had a couple questions myself. Was phosphate supplementation permitted and/or encouraged on these studies?

DR. TOOLE: Yes, it was, and in the 687 patients that received a 300 mg dose, there were 17 patients who received phosphate supplementation. In general, those were the patients who had the Grade 2 or higher abnormalities.

DR. GULICK: So, it was at the discretion of their primary physician whether to add it.

DR. TOOLE: True.

DR. GULICK: Did the protocol recommend phosphate supplementation?

DR. TOOLE: In the event of a Grade 2 or higher abnormality. It did not specify, but it recommended phosphate supplementation.

DR. GULICK: You showed us the intent-to-treat analysis and then an as-treated analysis for Study 902 to try to address the fact that a certain number of people actually changed their background medications.

Do you have the as-treated analysis for Study 907 also? I don't recall seeing that.

DR. TOOLE: I didn't show it because the as-treated analysis for Study 907 is almost exactly the same as the intent-to-treat analysis, because again, there were so few patients who changed their background regimens during the course of the first 24 weeks compared to Study 902.

DR. GULICK: We found on ACTG359 a significant PK interaction with adefovir and saquinavir that has never been fully explained.

Was an interaction between tenofovir and saquinavir formally looked at?

DR. TOOLE: We did not look at saquinavir. We chose the two protease inhibitors indinavir and

the lopinavir/ritonavir combination. We did not see an interaction with indinavir.

DR. GULICK: In the background materials, it talks about some of the ways that you are proposing to look at long-term safety. One of them is to look at the expanded access program over time.

Could you tell us what the commitment is to follow patients on the expanded access programs, let's say, after the drug is approved?

DR. TOOLE: Most of our safety follow-up is going to come from Study 910. In that study, we enrolled 575 patients who were previously randomized in the Studies 901, 902, and 907. Those patients will be followed until December of 2002, at which time we will have over two years of follow-up and more than 450 patients.

We are not going to sort out any patients in the expanded access population that will be followed separately from the rest of the other patients.

DR. GULICK: Lastly, in vitro, the presence of an M184V mutation is associated with an increased virologic effect, but apparently didn't see this clinically. Do you have a reason why that

might be?

DR. TOOLE: Actually, in the absence of TAMs, the M184V was associated with a significant increase in tenofovir, in the DAVG24, however, approximately 70 percent of patients in our studies were also expressing TAMs, and in that broader population M184V made no difference.

DR. GULICK: Thank you.

I am going to go back to a couple of people. Was that a follow-up, Vicki? Yes. Dr. Johnson.

DR. JOHNSON: You can call me Vicki.

[Laughter.]

In the first slide that Dr. Miller went up and showed, that gets to Chips, Trips--I am sorry--

DR. GULICK: You can call me Dr. Gulick.

[Laughter.]

DR. JOHNSON: Table 419, back on this M184V effect, this best reduction of 0.97 logs compared to all patients at 0.59, the p-values presented for heaving M184V alone versus placebo, what is the p-value for having M184V versus the all-patient group?

Could you just go back over that, because I think it gets to the question do clinicians need

to keep their patients on 3TC or not, if they are treatment-experienced, knowing that, as you have just said, 70 percent have one TAMs that sort of negates this effect.

DR. TOOLE: The analysis, which did show a statistically significant effect with the presence of the M184V, was in the absence of TAMs, and that p-value was 0.03. In the presence of other TAMs, the effect was not statistically significant.

DR. JOHNSON: So, what would be your recommendation with regard to--maybe we will discuss this later--indication, should clinicians keep their patients on 3TC to get this effect?

For treatment-experienced patients, it seems that the continuation of 3TC is not required.

DR. GULICK: We may want to address that in the afternoon some more.

I am going to go back to some people who asked to ask some more questions.

Dr. Bone.

DR. BONE: Thank you. I do have several additional questions. We talked earlier about the available histological information from the monkey studies, that you have necropsy data from your dog and rodent studies, I believe, and you saw the

histologic abnormalities that were similar at the higher doses.

Did you find no-effect dose for the osteomalacia changes in dogs or rats?

DR. TOOLE: I will let Dr. Bischofberger address that question.

DR. BISCHOFBERGER: I would like to clarify something first. The monkey, at the 10 mg/kg dose, 4-fold the human exposure. You are correct, we don't have any histological no-dose effect, but those animals did not have any hypophosphatemia, no glucosuria, no proteinuria, and all those three things were present at the higher dose.

So, with regards to the rats and dogs, we do have no-dose effects. In each case, they were at the lower dose than the one that showed the abnormalities.

DR. BONE: What multiple of the human dose?

DR. BISCHOFBERGER: In the dog, we saw bone abnormalities at 30 mg/kilo. That is 10-fold the human exposure. The next lower dose that was used was 10, so it's one-third of that.

In the rat we saw bone abnormalities at

1,000 mg/kilo, which is about 20-fold the human exposure. At the next lower dose, the 300 mg, we saw minuscule, but statistically significant changes, and at the 100 mg/kg we saw, that was the no-effect level with regards to bone abnormalities.

DR. BONE: How well did the histologic or did you formally analyze the relationship between histologic abnormalities and the clinically observable information, such as serum phosphorus levels?

DR. BISCHOFBERGER: You mean did we do correlations?

DR. BONE: Yes.

DR. BISCHOFBERGER: No. You have to understand the first observation of bone abnormalities was in these monkey efficacy studies, which were done at the University, so it wasn't even done at Gilead, and they were not toxicology or GLP studies.

Only once we became aware of those effects, we instituted in our then ongoing chronic tox studies, bone monitoring, so in many cases, the baselines were actually not here. The effects were really small that we saw.

I also want to comment on Dr. Farrelly

presented the PTH was up. That is, in general, true, but the data were highly variable. I think if you had to guess overall, you would say PTH would trend up, but there was no dose response, and it was statistically significant only at certain time points, and not at others.

DR. BONE: Did you do tetracycline labeling at the end of study for the dogs and rats in order to do formal histomorphometry on necropsy?

DR. BISCHOFBERGER: No, we did not, not in those studies.

DR. BONE: Did you obtain samples that could be assayed for 1,25-dihydroxy vitamin D when the animals were sacrificed?

DR. BISCHOFBERGER: We did assay for 1,25-dihydroxy vitamin D, but again, the data were variable, and I would say overall there was no change neither statistically nor even numerically.

DR. BONE: We saw that the dog did show, although the exact numbers weren't given, the 1,25 was low. I guess I would be interested in seeing the actual data presented for the rat and any human or dog data that you have for the 1,25 dihydroxy D, rather than just having a general statement, if we could do that.

DR. BISCHOFBERGER: I don't have a slide with me, but I can certainly get those data to you today.

DR. BONE: Thank you. The other question, a couple more questions, do we have any information about magnesium status in either the animal or human studies?

DR. BISCHOFBERGER: We looked at magnesium in the animals, but there were no changes in serum magnesium.

DR. BONE: You just measured total serum magnesium levels?

DR. BISCHOFBERGER: That's right.

DR. BONE: You didn't do anything else.

DR. BISCHOFBERGER: No.

DR. BONE: That is not very sensitive. Okay.

In the BMD studies that you have performed, it looked as though you had some mostly lumbar spine studies and a few femurs. Do you have any measurements in predominantly cortical areas, such as the forearm?

DR. TOOLE: No. We measured BMD changes in the spine and hip in Study 907, and in Study 902, just the spine.

DR. BONE: But no cortical, no measurements from forearms, for example?

DR. TOOLE: That is correct. Is Dr. Genant available?

DR. BONE: The reason I ask is it tends to be, particularly the ones at radial site, has a much higher proportion of cortical bone, which is where you described your histologic abnormality.

I think that is all my questions for the moment.

DR. GULICK: I had forgotten, unfortunately, Dr. Lukert, who has been patiently listening. Again, I am not sure she can speak to us. If you can, we would be happy to entertain your questions, and I apologize for overlooking you.

She can't right now. Okay. Thanks.

Dr. Pomerantz.

DR. POMERANTZ: Two questions. One of them, clinical, I want to extend Dr. Wood's question from the past about looking at subgroups. Clearly, there are people now on HAART that have inagnatic [?] osteonecrosis and also those that are on chronic steroids. The committee, I am sure, is going to be getting more into small groups of

people, if the drug goes into the community, that may be hurt by this.

Do you have any data on those groups or even anecdotal data in the large number of patients with problems with fractures or such, do you see anything or do you have any data on people who are on steroids who have the HAART-associated osteonecrosis?

DR. TOOLE: There was one patient on the study that, before entering the study, had a history of avascular necrosis, and this patient had a total hip replacement, and one month after had a fall and fractured his femoral neck. That is the only one we had.

DR. POMERANTZ: And none of these people were on chronic steroid use of any type?

DR. TOOLE: I don't recall the patient's history, I don't believe he was, though.

DR. POMERANTZ: The second one if more virological. We talked a little bit about the high-end research. I was interested in the low end in residual disease, and you had a number of people that went undetectable as defined by less than 400 and then more stringently less than 50.

There is some question in the durability

of those effects based on different drug combinations. What I am referring to is the blips or spikes that can take place in some of those patients.

Doug Richmond feels that if there is no effect on short-term mortality and morbidity, there is some data from other groups that that may not be the case.

Did you monitor those people who went to less than 50 or less than 400 over your year studies to look for blips of spikes back in the detectable range?

DR. TOOLE: We didn't do that. I think the FDA presented the graph representing those changes to less than 50 or 400, but predominantly, those patients who achieved less than 50 or 400, those changes were variable [?], certainly through the course of 24 weeks.

DR. POMERANTZ: So, during that time when you monitored these people, you had no patients that blipped or spiked?

DR. TOOLE: There may have been a few patients, but there weren't enough patients that would require any--

DR. POMERANTZ: Okay. Thank you.

DR. GULICK: Any other questions from the committee? Dr. Yogev.

DR. YOGEV: I was intrigued by your in vitro data, that there is almost a 10-fold increase in IC50 for the PBMC, the mononuclear cells versus the MT2, and then also dendritic macrophages, and I couldn't find what was the IC50 for those.

DR. TOOLE: I will let Dr. Bischofberger address that question.

DR. BISCHOFBERGER: The qualitative answer is that the tenofovir is more potent in general in macrophages than it is in lymphocytes.

DR. JOHNSON: Is he asking why the IC50 is higher in the MT2 cell assay?

DR. BISCHOFBERGER: If I could get 409.

DR. JOHNSON: It is a viral cytopathic effect assay. It would require higher concentrations.

DR. BISCHOFBERGER: Reproducible, the question that you asked.

[Slide.]

This shows anti-HIV activity in MT2 cells and PBMCs, and in monocytes, macrophages, and you see that the IC50 is 0.4 versus 0.63, and MT2 is 0.12 and PBMCs, and that is consistent with the

fact that macrophages are, in general, resting cells. They need thymidine kinase to activate nucleosides. Tenofovir is a nucleotide, and doesn't have to undergo that activation pathway.

DR. POMERANTZ: Just a comment on that because I think that is good point, but if you had done that in initially quiescent PBMCs, as some groups have, you might have seen it closer to what you see in macrophage monocytes.

DR. BISCHOFBERGER: That is exactly right.

DR. POMERANTZ: And then hit them with PHA and IL-2 after they have seen the drug for a couple of days, you might had a different effect.

DR. BISCHOFBERGER: That was actually a study that was published in PNES by Imbach and colleagues, and they found exactly that. Thank you.

DR. YOGEV: The second question, the hydroxyurea addition, amazingly almost 20 to 30 times more activity of tenofovir, and then you claim in 901, you didn't see it when you use it only on 75 mg, and when you look at the data with the small number that you have, it is almost double the amount of viral load decrease from 0.22 to 0.44, something like that.

Do you feel comfortable that it really didn't approve itself clinically or because of the low number and using the lower dose, you did not pursue correctly this?

DR. TOOLE: I think the change that we saw in the 75 mg cohort that received either no hydroxyurea or hydroxyurea concomitantly didn't warrant further evaluation when we consider the changes that we observed in the 300 mg dose group.

DR. YOGEV: By itself.

DR. TOOLE: Did not.

DR. YOGEV: By itself, but you did not use hydroxyurea with 300 mg?

DR. TOOLE: Correct, we did not.

DR. GULICK: Dr. Schapiro.

DR. SCHAPIRO: One question is just regarding the 907, why was it limited to 10,000 copies?

DR. TOOLE: We wanted to prevent the corruption of the primary efficacy endpoint by a lot of background switching. In Study 902, we allowed patients to enroll with viral loads up to 100,000, but in that study, about 30 percent of patients changed their background regimen during the course of the first 24 weeks in an effort to

minimize that switching and also to make it more amenable to investigators and their patients who may be randomized to placebo for 24 weeks, we restricted the upper viral loads limit to 10,000 copies.

DR. SCHAPIRO: And the other question, I don't think we saw the correlations between the TAMs and the phenotypic changes. Do we actually have it? On the Virco study, there are 20 such patients, and there were others in the additional studies. That data which we usually see, which shows these mutations to this fold change, we didn't actually see those, we just saw data which shows it as a group.

What we usually look at is we see various accumulations of TAMs and what they do. Do you have that type of data?

DR. TOOLE: I will let again Dr. Miller address that.

DR. MILLER: May we have Slide 75, please.

[Slide.]

These are the results then looking at the specific number of TAMs, just the aggregate out of the 6 and the baseline, and the susceptibility to both tenofovir and zidovudine. As you can see

that, 110, the susceptibility to tenofovir is 0.8, and it looks like it is increasing with increasing numbers of TAMs, greater than or equal to 4, there is reduced susceptibility of 2.8-fold to tenofovir.

In contrast, the zidovudine levels are notable even at just 2 TAMs, increasing up to 19-fold resistance.

Perhaps more interesting is from Slide 360.

[Slide.]

It is looking at the specific patients in the integrated analysis of Studies 902 and 907 for whom we had baseline phenotypic data, and this is then the same stratification by number of TAMs, presence or absence of the M41L and L210W mutations.

If you just look at the far right column, you can see no TAMs, and then one or two TAMs, three or four TAMs, showing a decreased susceptibility up to 2.6-fold, and then when you stratify based on the presence or absence of the 41L, the 210W, you go from 2.8-fold reduced susceptibility to 1.7-fold in the absence of the 41 or 210W.

So, the results appear very consistent

between the genotypic and phenotypic, and the clinical trial results.

DR. SCHAPIRO: You don't have though actually, as you were saying here before you wanted for the 210, you don't actually have the genotypes with the phenotypes for these.

You are just sort of lumping the TAMs together and then showing us the analysis. You don't actually have the data that shows the genotypes and the phenotypic correlate--actually, in that last slide you showed--

DR. MILLER: The last slide, I think the last two lines of the last slide. We can show that again.

DR. SCHAPIRO: Could we see the last slide again?

DR. MILLER: 360.

[Slide.]

DR. SCHAPIRO: The three TAMs plus, that can be anywhere from three to six mutations, and the one below it can only be three or four mutations. So, that is a little bit of a biased analysis since we know that accumulation also affects it.

You are only allowing the maximum TAMs you

can have is four, if you don't have four, you wanted 210, whereas, in the line above it, it can be up to six.

DR. MILLER: The mean number is very similar actually. I don't have the actual number because as you might be aware, there are specific patterns of mutations, and they tend to top out at around three or four, and we rarely have five or six mutations actually in any individual patient. We have not done the specific, I think analysis, you are referring to is simply to add the 41 or 210 mutation in the context of a site-directed recombinant virus or something like that.

This is very new information for us. It is a pleasure to discover in these exploratory analyses, and we will be following up on that certainly.

DR. GULICK: If there are no other burning questions at this point from the committee, why don't we stop here. It is 12:15. We will break for lunch until 1:10, at which time we will resume.

Thank you, everyone for a good morning.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to be resumed at 1:10 p.m.]

AFTERNOON PROCEEDINGS

[1:25 p.m.]

DR. GULICK: We want to do a couple of things in follow-up to the morning.

Dr. Lukert, can you hear us? I will take that as a no. I wanted to give her the opportunity to ask any questions, and she didn't get that opportunity this morning. We will see if she gets back on in the next minute or so.

We wanted to give the sponsor an opportunity to follow up on some of the questions and points that were raised this morning. I see Dr. Bone joining us.

DR. TOOLE: First of all, with regard to an earlier question, looking at the DAVG24 in Study 907, with regard to patients who had more than or less than four previous antiretroviral agents, for those patients who had more than four prior agents, the change in the placebo group was minus 0.2, and the change in the tenofovir group was minus 0.56 log reduction, and that difference was highly statistically significant.

Secondly, regarding Dr. Yogev's question, were the percent of patients that went below 400 copies/mL, who enrolled in Study 907, with baseline

viral loads greater than 5,000, there was zero in the placebo, and 15 percent of patients in the tenofovir arm, and that was significant with a p-value of 0.008.

Dr. Bone, regarding your question of cortical bone mineral density, I would now like to invite Dr. Harry Genant to join us to telecon. Dr. Genant is Professor of Radiology, Epidemiology, Medicine, and Orthopedic Surgery, and Executive Director of the Osteoporosis and Arthritis Research Group with the University of California at San Francisco.

He has also chaired and published recommendations from a World Health Organization-sponsored task force on osteoporosis.

Dr. Genant.

DR. GENANT: [By telephone] Good afternoon. Are you able to hear me?

DR. GULICK: Yes.

DR. GENANT: Fine. Dr. Bone asked the question with regard to measurement of a cortical bone site, such as the forearm, and that is an important question. In the two pilot analyses that were done in 902 and 907, forearm was not measured, but the spine was measured in 902 and 907, and the

hip was measured in 907, as well.

Of course those are the two most important anatomic sites, and from the hip itself, one can generate information that is relevant to cortical bone, particularly in the total hip measurement, but at that site, given the numbers of patients studied, there were no significant changes.

DR. BONE: Harry, this is Henry. How are you?

DR. GENANT: I am doing fine, thank you.

DR. BONE: Good. Wouldn't you think that going forward, the forearm would be something that ought to be looked at as we go along?

DR. GENANT: Yes, I think that if one does begin to see significant changes at the spine and/or hip, that the forearm, as a measure of non-weight-bearing cortical bone, would be of interest.

I do believe that from the hip measurement itself, one can extract a purely cortical measurement from the sub-trochanteric area that will give essentially a cortical measurement, although it is a non-standard technique.

DR. BONE: I don't think any of the standard instruments would give that as one of the

standard readings.

DR. GENANT: That is correct, although it can be extracted from the routine acquisitions.

DR. TOOLE: Can I suggest that we will pursue this also in the questions for the committee.

Dr. Bone, regarding your question that we are observing small changes in the fractional secretion of phosphorus and how do those translate in changes in serum phosphorus, if I could have Slide 255, please.

[Slide.]

Shown here are the median changes from baseline in serum phosphorus measured for the placebo group and the tenofovir 300 mg group in Studies 902 and 907. Through week 24, there was no significant differences in the serum phosphorus level between placebo and tenofovir 300 mg group.

With regard to your question of how many patients had changes of 0.5 mg/deciliter or more, that would be corresponding to here. Whenever those changes occurred, they occurred in a similar number of patients in the placebo group and the tenofovir group.

DR. BONE: I am sorry. Could you go back?

DR. TOOLE: This is the median and the interquartile range. So, 25 percent of patients had a change of 0.5 mg/deciliter or more in serum phosphorus, however, these changes were similar in the placebo group and the tenofovir group.

Slide 254, please.

[Slide.]

This now looks at the long-term data following patients out for more than two years, and again, the changes that were observed over two years were consistent with what was observed in the course of the first 24 weeks.

DR. BONE: Again, what you are showing here is the median changes. What about the patients who showed a small change, small decline?

DR. TOOLE: These are medians with the interquartiles, so the patients who had a change of a decrease of 0.5 mg/deciliter or more would be the lowest 25 percent of the patients, however, 25 percent of the patients in the placebo group also had a similar change during the first 24 weeks of the studies.

DR. BONE: Thank you.

DR. TOOLE: Lastly, I would like to invite our consultant Dr. Steve Teitelbaum. Dr.

Teitelbaum is the Wilmer and Roswell Messing Professor of Pathology and Immunology at Washington University School of Medicine in St. Louis. He is Chairman of the Institutional Review Board at Barnes Jewish Hospital and the past President of the American Society for Bone and Mineral Research.

DR. LUKERT: I would like to ask a question about the phosphate supplement. When you started phosphate supplements, did you start after the first abnormal phosphorus or after the second abnormal serum phosphorus?

DR. TOOLE: That was variable. There were 62 patients who had Grade 2 or higher hypophosphatemia. Among those 62 patients, 11 used phosphate supplementation at the onset of the hypophosphatemia.

DR. LUKERT: Did they just correct, or what happened to their serum phosphorus?

DR. TOOLE: The serum phosphorus corrected whether or not the patients received supplement in that group of patients.

DR. LUKERT: What would have happened in those patients that didn't receive?

DR. TOOLE: In the 51 patients who didn't receive phosphate supplementation, they also had at

most two visits with the abnormality.

DR. LUKERT: Did you ask about bone pain?

DR. TOOLE: There were two reports of bone pain, and in each case, those were transient and related to recent traumatic event.

DR. LUKERT: Were questions specifically asked about long bone pain?

DR. TOOLE: There was no solicitation by the investigators for the incidence of bone pain, no. The investigators, however, were asked to inquire about any possible fracture which would be secondary to an emergency room visit, so we captured as much data as we could regarding bone fractures.

DR. GULICK: Other questions, Dr. Lukert?

DR. LUKERT: No. Thank you very much.

DR. GULICK: Thank you.

At this time, I would like to turn it over to Dr. Teitelbaum.

DR. TEITELBAUM: Thank you. Good afternoon, ladies and gentlemen.

With Dr. Bone's forgiveness, I just want to brief the panel about some definitions of bone biology and bone pathology, because I think it puts in perspective the lesion that we are purporting to

be looking at.

When most of us think of systemic bone loss, we think in terms of the disease osteoporosis, and I just want to be sure that everybody understands that we are not dealing with osteoporosis here. Osteoporosis, by definition, is a decreased mass of normal and mineralized bone.

We most commonly see it following the menopause, and what happens in osteoporosis is that the bone resorptive cell, the osteoclast becomes overactive, if you will, it degrades bone at a much more rapid rate than it is being made, and it is being made at least the normal rate.

Now, in osteomalacia, what happens is bone is being made normally. Bone matrix, the organic matrix of bone is synthesized normally, but there is a defect in its mineralization. So, what happens is the unmineralized bone matrix accumulates. It accumulates because it cannot be mineralized in the setting in which it finds itself.

I will return to osteomalacia in a moment, but just parenthetically want to say that osteonecrosis, on the other hand, is a very different phenomenon. What osteonecrosis

represents is actually death of bone, and the most common circumstance which you see it is in prolonged glucocorticoid therapy.

Now there is compelling evidence this is, in fact, due to enhanced apoptosis of bone-forming cells and osteocytes, but let's return, if we will, to osteomalacia.

As I am sure Dr. Bone and Dr. Lukert will agree, osteomalacia is a disease that bone doctors love to see, and it is the disease that bone doctors love to see because we can cure it, and we are much more effective in treating osteomalacia than we are in curing osteoporosis.

There are a variety of causes of osteomalacia, but clearly the most common one in our society is hypophosphatemia. Now, you will note that I did not say hyperphosphaturia. I am talking about hypophosphatemia, because at the end of the day, what really counts here is not how much phosphate is being excreted in the urine or being absorbed from the gastrointestinal tract, it is how much phosphate the bone sees.

If the circulating levels of phosphorus are normal, the patient will not develop osteomalacia. A question came up, Dr. Bone raised

the question about the histology of the monkeys that received four times the dose of the drug, and it is a very good question, but I want to point out that those animals were not hypophosphatemic, and them not being hypophosphatemic really is prima facie evidence that they did not have osteomalacia.

If I can just stress once again, what we are really asking the question about is not hyperphosphaturia, but whether or not there is an impact on the circulating levels of phosphorus, and I think the data substantiate the fact that this impact is not substantial.

I have, in fact, looked at the bone of the monkeys with osteomalacia, and they did, in fact, have severe osteomalacia, but what was really striking about it, and which is a paradigm for the human disorder, is that it is completely reversible.

When the parallel monkeys came to necropsy, the osteomalacia was completely healed, and that is what we see in man, and there are two examples that I would like to discuss with you. One is the disease known as oncogenic osteomalacia, and an oncogenic osteomalacia is patients who specifically have mesenchymal tumors. They have

severe enhanced excretion of phosphorus in the urine, they develop severe osteomalacia. You find the tumor, you excise it, and they completely normalize.

The other example is patients who have excessive antacid therapy. They are binding phosphorus in the gut, they can develop severe osteomalacia, we encounter them not infrequently. We take them off the antacids, we phosphate supplement them, and they completely normalize.

So, the point that I want to get across to you is we are not dealing here with an irreversible disorder should it exist, should it exist, and there is really no evidence that it does exist in these treated patients, but in the worst case scenario, this is not an irreversible disease.

Now, I want to close by just talking about what the possible worst case scenario is. Let's assume that we have a patient who, for some bizarre reason, takes the amount of this drug that Jib Gilead gave to the monkeys, and develops a severe osteomalacia that the monkeys developed.

Well, this would be detected, the patient would be taken off the drug, phosphate supplemented, and completely cured. But I want to

close with that point, that we are not, in fact, dealing with an irreversible disorder.

Thank you very much.

DR. GULICK: Thank you, Dr. Teitelbaum.

I want to hold further discussion on these points until we get to the actual questions.

At this point, I want to turn to the open public part of the hearing. We have had four speakers who have signed up, and I would like to invite them to take the podium. The first person to have signed up is Dr. Yvette Delph, who is from the Treatment Action Group.

Dr. Delph, wherever you feel comfortable, back there or up here, as you like it.

Open Public Hearing

DR. DELPH: Good afternoon, ladies and gentlemen. Thank you for allowing me to present the position paper on the accelerated approval of tenofovir DF.

My name is Yvette Delph, and I am the Antiviral Project Director for the Treatment Action Group, which is a community treatment activist organization. The copies of the TAG position paper are on the back table, and they have some extras for anyone who may need them. I think each of the

members of the committee should have received one from me earlier today.

First of all, I would like to very highly commend the sponsor Gilead for conducting pivotal registrational trials of tenofovir DF in such highly treatment-experienced individuals. Tenofovir DF has a highly favorable resistance profile both in vitro and in vivo, and has demonstrated its efficacy against multinucleoside-resistant HIV.

Administered as one tablet, once a day, tenofovir DF makes a substantial contribution to the simplification of antiretroviral regimens. Since tenofovir inhibits HIV-1 reverse transcriptase at concentrations that are approximately 3,000-fold lower than that needed to inhibit DNA polymerases beta and gamma, it has very low potential for mitochondrial toxicity and, to date, there has been no evidence of mitochondrial toxicity due to tenofovir DF in clinical trials.

Tenofovir DF has a favorable side effect profile and both in Studies 902 and 907, the occurrence of clinical events and laboratory abnormalities in the 300 mg daily arm was similar to that in placebo.

There is no hepatic metabolism of tenofovir and it is excreted unchanged in the urine by the kidneys. Thus, there is potential for interaction with other drugs that are renally excreted and there is likely to be a need for dosage adjustment in individuals with renal impairment. Tenofovir is not a substrate, inhibitor, or inducer of the cytochrome p450 family of liver enzymes. It therefore has a low potential for drug-drug interactions involving this family of liver enzymes.

Tenofovir DF has been studied in very few persons with viral loads over 50,000 copies/mL. Therefore, there are not enough data to assess the efficacy of tenofovir DF in this population. Because of earlier concerns that we have heard about bone toxicity, tenofovir DF has not been studied in children to date.

The Treatment Action Group is in favor of accelerated approval for tenofovir DF for use in combination with other antiretrovirals in the treatment of adults with HIV infection.

The FDA should require the sponsor to complete the following studies in the postmarketing period:

A safety and efficacy study in individuals with viral loads over 50,000 copies.

A safety and efficacy study in treatment-naive individuals, and such a study (903) was fully enrolled in January 2001. In fact, looking at the demographics that were presented thus far for the patients who were enrolled at baseline, the median baseline viral load was, in fact, close to 100,000.

Safety and efficacy studies and pharmacokinetic studies in children.

Safety and pharmacokinetic studies in individuals with renal or hepatic impairment.

Studies to identify long-term toxicities of tenofovir DF, and in particular also, to follow more closely the potential for bone toxicity in individuals.

Drug-drug interaction studies with drugs that inhibit renal tubular secretion such as trimethoprim or cotrimoxazole which includes trimethoprim, and probenecid, drugs that are excreted by the kidneys and are likely to be used concomitantly by some HIV-infected individuals, such as stavudine, certain antibiotics including aminoglycosides, cephalosporins, and penicillins,

narcotic analgesics, such as demerol and morphine, lithium and digoxin, and the studies which the sponsor has indicated that it plans to conduct with ddI EC, methadone, oral contraceptives, and adefovir.

We also need more data on the clinical correlation or we need data, because there are none, on the clinical correlation of the IC50 or IC90 with plasma levels of tenofovir.

There are several additional issues that TAG wishes to raise:

Gilead is the first sponsor to respond to the calls from the community to study investigational agents in highly treatment-experienced individuals and should be congratulated, not penalized, for this.

TAG is however concerned that a 48-week dose-finding study was conducted in individuals, virtually all of whom had HIV resistance to at least one class of antiretroviral agents and many who had resistance to more than one class. The FDA should require sponsors to determine the appropriate adult dose for antiretroviral agents before proceeding to large Phase III studies, especially in individuals with limited treatment

options.

There is not yet enough evidence that tenofovir DF should be used only with nucleoside reverse transcriptase inhibitors. Until there is more evidence, tenofovir should be used in conjunction with at least one protease inhibitor or a non-nucleoside reverse transcriptase inhibitor and at least one nucleoside reverse transcriptase inhibit.

Some have questioned whether broad approval for tenofovir DF should be granted when the data submitted to date focus on experienced individuals. Here are several reasons why TAG would urge the FDA to grant accelerated approval for the use of tenofovir DF in combination with other antiretrovirals, in the treatment of adults with HIV infection.

Precedent. Since the 1995 approvals of lamivudine and saquinavir, the FDA has used this language for approving new antiretroviral agents even though pivotal studies were not done in certain important HIV-infected populations.

Although some thought that these broad indications would let industry off the hook for postmarketing studies, both Glaxo and Roche

continued developing 3TC and saquinavir respectively, unlike that which Roche did with ddC after 1992. With the advent of HAART, these additional indications proved very useful.

Timing. Gilead did not have 24-week pivotal data on naive patients in May 2001 when it submitted the NDA. However, its pivotal study in treatment-naive individuals fully accrued in January of 2001, and so 24-week data is likely to be available within a few months, possibly early in 2002. Gilead could not, therefore, avoid doing the necessary study in naive individuals postmarketing. It has already been done.

Logic suggests that if the drug reduces HIV RNA by about 0.6 log, in treatment-experienced individuals, it will reduce viral load by even more in naive individuals.

Safety data are available in both populations in real time; to date there has been no serious safety problem in either population. In fact, tenofovir DF has a very favorable safety profile in the treatment-experienced, the population for which the safety data have been analyzed. In fact, the population for which toxicities are often even more of a problem than in

the naive population.

Weight of Evidence. Cumulatively, the drug has good potency, a favorable resistance and safety profile. It is easy to take and generally well tolerated.

Finally, consistency. For years, the community has been asking industry to study new drugs in experienced patients, as well as in naive patients. Unlike Abbott, which is a giant pharmaceutical company with lots of resources, which could therefore submit an NDA for lopinavir/ritonavir containing pivotal data on naive and experienced patients, Gilead is a relatively small company with fewer resources.

We might wish Gilead had studied both populations in parallel, but they had just had a setback with adefovir and had been required to get 48-week safety data for tenofovir DF for renal and bone toxicity. We should not penalize them for going sequentially.

Also, I would like to note that the community is concerned that if a very limited indication for treatment-experienced individuals only is given, then, access by treatment-naive patients for off-label indications may be

restricted.

We are concerned that HMOs, ADOX, Medicaids, and so on, may not be willing to provide drug for an off-label indication for naive patients. While we recognize that the situation may be favorable in states like New York and California, very different circumstances may apply in certain other states like Texas, Alabama, or Georgia.

I would also like to ask Gilead to analyze Studies 902 and 907 data, to look at outcome based on the number of classes of antiretrovirals to which subjects are resistant at baseline.

If anyone needs more information or wants a full statement electronically, it is available on the web site for the Treatment Action Group, which is www.treatmentactiongroup.org.

Thank you very much, Mr. Chairman.

DR. GULICK: Thanks, Dr. Delph.

The next speaker is Mr. Brett Grodeck, who is from Santa Monica, California.

MR. GRODECK: My name is Brett Grodeck. I am here not to give a rigorous scientific explanation of tenofovir. I am here to talk about what it is actually going to do in the community

when it is approved.

[Slide.]

Just to give you some background, I am formerly editor of Positively Aware, formerly managing editor of HIVandHepatitis.com, and I work with the Rand Corporation in Santa Monica, California. I also have some background in pharmaceutical public relations. I bring this up for a reason I will get to in a moment.

[Slide.]

My purpose for speaking here is really to talk about a side effect of tenofovir, something I haven't read much about, haven't heard much discussion today, but I consider it an important aspect of the approval of tenofovir in real life.

I am asking the FDA to consider the long-term effects of tenofovir on the hepatitis B virus. Obviously, I would like to call for more long-term research, some short-term actions, and what I would like to do is try to give some contextual perspective to introducing tenofovir into the real world.

[Slide.]

I am sure some of you are asking why this is relevant to approving tenofovir for HIV

infection, but in the real world, and in some cases up to 10 percent of HIV-positive people in the United States are also coinfected with the hepatitis B virus.

That number is probably high, but these are essentially the same people. They are in the same risk group, and they can jump from group to group.

Also, coinfection with HIV and hepatitis B ultimately results in greater liver damage. I have given the committee some background material. Again, I understand it is not the scientific rigor that you are probably accustomed to, but from somebody who, in fact, has HIV and chronic hepatitis B, and is taking tenofovir, it is kind of this real world situation that I would like you all to consider.

Obviously, we have all heard reports of liver damage rising in HIV population. Sometimes I have to ask what is the point of approving more drugs for HIV when we are seeing more and more liver damage. We are keeping people alive in order to see them die of cirrhosis, liver complications.

I am also here to represent a very undervalued group, and that is people with chronic

hepatitis B. I understand that hepatitis B probably doesn't have the kind of media value that, say, hepatitis C or HIV has. It is an old disease, it has a vaccine to prevent it. It is probably most prevalent among drug users. So it doesn't make for good headlines, it doesn't make for good press.

But my question is - so many people with HIV are seeing liver complications. We are ultimately being forced to make a choice between dying of HIV or dying of liver disease. The way I see it, dead is pretty much dead however you get there.

[Slide.]

I am sure you are all familiar with lamivudine. Clearly, it was a blockbuster for its maker, Glaxo. Also, gets some recycled profits from that by clearing it for hepatitis B. I am sure a lot of you are familiar with entire process, but now, so many years after it has been approved, we are seeing what happens to lamivudine when it is introduced again into the real world.

Studies have shown that in HIV-positive people, hepatitis B virus, resistance develops in about half of people who take 3TC, lamivudine, and

after four years, 90 percent of those people will develop resistance. That is hepatitis B resistance among HIV-positive people.

I have also read recently that the transmission of lamivudine-resistant hepatitis B virus is being transmitted into areas of the world where lamivudine has not been formerly introduced. What that means is you can probably transmit resistant virus.

So, so many years down the road, so many approvals later, what have we learned from treating HIV? Clearly, monotherapy for viruses don't work. We see it in hepatitis C, we are seeing it in hepatitis B, and I am sure in other areas. Multi-drug combinations are really the only way to fight a virus in the long term.

We also know from treating HIV and hepatitis B that drug companies can still make their profits before completed combinations are available to the public. We introduced AZT, we introduced ddC, ddI, d4T, and 3TC all before they were paired up to make a potent combination. We are doing the same thing with hepatitis B right now, and we are seeing the same thing, but no one seems to be bringing it to the front.

[Slide.]

I think it is important for you and everyone here to know about adefovir. Clearly, adefovir, clearly, Gilead has had a role in the HIV community. I think they have tried to participate. They have done some good things, they have done some things that the community may not have liked, but ultimately, adefovir for HIV was flawed, it didn't work, and I know that Gilead kind of feels burned by the HIV community. I think there is also sort of a subtle fear of adefovir among the community, among patients, which may be some of the reason why Gilead is trying to distinguish adefovir from tenofovir in terms of HIV and hepatitis B.

I think it is great that Gilead is pursuing adefovir, it is in Phase III. It is very promising, it is probably the most promising if you have chronic hepatitis B. That is really the only thing to look forward to if you have resistant lamivudine virus.

So far the data has reported there hasn't been any resistant hepatitis B virus, but as we all know, it is just a matter of time.

[Slide.]

I am not a scientist or a doctor, so I

can't really take you through the intricacies of the science here. I have brought a couple of slides that have some things that anyone can look up on the web.

I will tell you my own personal experience. As I mentioned, I am HIV-positive. I have chronic hepatitis B. I did my own research and discovered that what was only available to me at the time was tenofovir. My HIV was completely under control, it hasn't been a problem for years. My hepatitis B was out of control, and I really had no recourse. I could not get into an adefovir study, and my liver enzymes were rising. I was between a rock and a hard place.

I researched it and discovered that tenofovir has significant activity against hepatitis B virus. Because I am HIV-positive, I qualified for the expanded access trial. I got tenofovir. I have been taking it for two months now. My hepatitis B viral load has gone from greater than 5 billion to 68 million.

Now, I can't tell you exactly what that means, and I can't tell you what that means in hepatitis B terms, but I can tell you that my liver enzymes dropped from 187 to 106 in two months, and

that is just because of tenofovir. I think it is important to consider that this is going on.

This is just your standard data, and the next slide is, as well.

[Slide.]

I wish I could interpret this last bullet for you, but again I don't have a science background, but I get someone here could, and could probably tell that tenofovir and adefovir probably have about the same activity against hepatitis B, at least it did for me.

[Slide.]

I think if you are all here to consider what tenofovir will do in real life, I would like to ask the committee to consider that it will be a blockbuster, it will be huge, something like Sustiva, and everyone will be taking it, everyone who is HIV-positive, and anyone who has chronic hepatitis B.

What you are doing is you are introducing it into a population where up to 10 percent of those people have chronic hepatitis B. I tried asking Gilead. I couldn't really get a clear answer, and I understand that it is complicated, I do understand that.

But what I think is important for the committee to consider is will introducing tenofovir into an HIV-positive population ultimately lead to the emergence of resistance hepatitis B virus in that population, and if so, will that resistant hepatitis B confer to adefovir.

I have a gut feeling that that is worth looking at, and I want to look into why has Gilead sort of not talked about its anti-hepatitis B properties. I don't know, maybe they are recouping losses from adefovir, from not being approved. I can't say, but it's worth talking about.

Finally, by approving tenofovir for HIV, what are you saying to the hepatitis B community, who has chronic hepatitis B today, are you saying that HIV-positive people somehow get this drug because their disease is more political, more important, are sort of white gay men getting drugs faster than typically drug users who have chronic hepatitis B? I don't know, I don't know the answers to those questions, but I think they are worth considering.

I also understand that Gilead is a small company relatively, and I understand the whole position of the small but well intentioned company.

Having work in pharmaceutical public relations, I know this line really well. I have written it into scripts and proposals, and it was sort of a standard phrase that I used, "small but well intentioned," both true and overstated.

I also know that in pharmaceutical public relations, I have cut checks to members of the HIV community, and I am sort of am proud of some accomplishments in terms of public relations having influenced the very committee that I am talking to today.

[Slide.]

Finally, I think tenofovir should be approved. You know, I didn't use it for HIV, I am using it for chronic hepatitis B. So, I hope it is approved, but I hope that the committee and I hope that the research communities, and I hope that Gilead defines tenofovir's role with hepatitis B, and they make that aware to the public easily accessible.

I think that the labeling for tenofovir should be strong, unlike the labeling in lamivudine. It's a side note, and, you know, side notes kill.

HIV doctors who are relatively

narrow-minded into the HIV world tend to forget that there are other diseases out there, and they are prescribing 3TC to people who may be coinfected. They may not even know, and they are wasting the drug.

I think this is also a really great opportunity for Gilead to take the lead in coinfection causes. I don't think it's an expensive option. I don't think this is something that is impossible to do. I think it is an arm of the marketing department to educate doctors and thought leaders about the coinfection strategies and issues.

That is it. Thank you.

DR. GULICK: Thanks very much, Mr. Grodeck.

MR. GRODECK: If anyone has any questions, thanks.

DR. GULICK: Thanks.

Our next person to sign up is Ben Cheng from Project Inform in San Francisco. That doesn't look like Ben.

DR. DELPH: Mr. Chair, Ben Cheng would like to apologize, but he had a plane to go and catch, so he has asked me to read his statement

instead.

DR. GULICK: Okay.

DR. DELPH: I will read it verbatim, so you may need to use your imagination here.

My name is Ben Cheng and I am the Director of Antiviral Advocacy at Project Inform, an HIV information and advocacy organization based in San Francisco. My organization and I have not received any funding from Gilead Sciences to be here today.

I am here today to support approval for tenofovir. The data that have been presented clearly demonstrates that the drug has convincing activity against HIV among antiretroviral-experienced patients, and what so far seems to be an exceptional level of short-term safety compared to most other HIV medications.

We are not concerned that the levels of viral load suppression and CD4 cell increase might appear meager when compared to some other classes of drugs since these data come exclusively from people with long prior histories of treatment use.

The results cannot fairly be compared to studies of other drugs in naive patient populations. Most important, these results suggest significant potency against most

nucleoside-resistant virus.

There is large and growing need for new compounds that can work despite prior nucleoside resistance. Even though the current data come solely from a treatment-experienced population, Project Inform supports an indication for tenofovir that is not limited to antiretroviral-experienced patients.

We feel that tenofovir should be approved widely for the treatment of HIV disease, similar to the indication other HIV therapies. No HIV AIDS drug that worked in experienced patients has ever failed to work in treatment-naive patients. On the contrary, in almost every known instance, they have worked better in the naive population.

While drug safety can be a consideration when giving a new drug to a naive population, that does not seem to be a factor here given tenofovir's excellent safety record to date.

Most HIV therapies have been tested primarily in naive patients, yet, have been given indications for all stages of HIV disease. This drug has been tested first in the more difficult setting of experienced patients, and it should be, if anything, easier for foresee good activity in

the naive population.

If tenofovir were only approved for experienced patients, then, there may also be problems in the future for some people in getting the drug reimbursed or problems accessing the drug.

Gilead Sciences should be applauded for taking the risk in conducting their studies among experienced patients instead of the normal drug development path of conducting studies in naive patients.

Many HIV community groups have long urged industry to conduct studies for antiretroviral-experienced patients. If tenofovir were to get approval only for antiretroviral-experienced patients, this could set a bad precedent that will likely result in industry returning to only conducting studies in naive patients. As a result, people with limited treatment options are the ones most likely to be hurt by this. End of quote.

Thank you, Mr. Chairman.

DR. GULICK: Thank you, Mr. Cheng.

Our last speaker to sign up for the open public hearing is Jules Levin from NATAP in New York.

MR. LEVIN: Hi, everybody. Many of you know who I am, Jules Levin, the founder and executive director of the National AIDS Treatment Advocacy Project based in New York City, NATAP for short. I am very proud of the work that NATAP does and the work that I do.

I have had HIV and hepatitis C for 18 years, and the primary mission of NATAP is to provide treatment education and information to people all over the world. That is what we do, for people who don't know what we do.

In particular, we provide a very wide and deep treatment education program for people in New York City, for people with HIV and for case managers and medical professionals. As a result, I come in contact and my organization comes in contact with thousands of people with HIV, literally, frankly, every day, and that is not an exaggeration.

So, I come here to speak to you for myself and I think for some of the concerns of people with HIV and hepatitis. So, I am going to be brief, I don't have a lot of explanations, I am going to raise a few points.

If you look at the safety and lab data

with regards to PMPA, tenofovir, ALT elevations don't seem to occur, it is kidney excreted, if not completely through the kidney, at least mostly through the kidney.

I think when we are talking about a Phase IV study, we need to explore the use of tenofovir in people coinfected with HIV and hepatitis C, both people who are naive to HIV treatment and people who are experienced, and we need a study that looks at biopsies to really see if there is a difference, not just in ALT elevations, but also in the liver itself.

Without doing a biopsy in such a study, the results will always be questioned, and I strongly recommend that that be required for a Phase IV study.

I think that this drug in a treatment-experienced population, this is a very important drug and people are waiting, and have been waiting, for this drug and other drugs like this who have resistance and are failing therapy, and have lots of treatment experience.

I think the resistance profile is very impressive, and I think that our population, this drug really needs to be approved pronto and in the

pharmacy right away.

I feel that my hand is forced to state my position today. I have some concerns about a first-line indication. To date, I know that there is a study going on in treatment-naive, it is unblinded. It is blinded at this point, and we don't have the data, and maybe we will have the data in a couple of months, and it probably will look good, but we don't have the data today.

The study looks at PMPA as a substitute for a nucleoside, so it efavirenz/3TC and d4T, or efavirenz/3TC and PMPA. Well, with a first-line indication, what about the doctor that wants to use PMPA, abacavir, and another nucleoside? We need a study. That is a Phase IV study that needs to be done.

Another point that I have a concern about, which we seem to be very unclear about today, and I would like Gilead and the panel, some very esteemed HIV doctors and researchers here on the panel to discuss this point, so that we could come away with a more clear indication about this.

That is with regards to the 184 mutation. Does the 184 mutation really improve the response to PMPA, and does 3TC therapy have to be continued

to do that? If you look at the briefing statement, I am glad the FDA--the FDA deserves a couple of compliments here, too--the FDA put the briefing statement, I think for the first time, on their web site, and I am pleased about that, so I read that because I didn't get a book, because I am not on the panel, and I think that the data on this question is unclear.

At the fourth resistance workshop, Gilead presented some convincing data that the 184 increased the response, and the question is was 3TC still present to maintain the 184. That question is uncertain. Maybe Gilead can answer this question, because there is a lot of data in the book, and it was discussed here about if the 184 is present, maybe it does improve response, but it didn't talk about how many patients were maintained on 3TC, and maybe the 184 was there with 3TC present or maybe without 3TC present. I don't know the answer to that, but there is a couple of resistance experts on this that I know that can direct this question.

One other point I would like to raise. I think that the point that was raised by Brett, I think can be addressed in labeling, and I would

like the panel and Gilead to discuss this, addressing this in the label, at least consideration of this question of addressing it in the label. Maybe we can have some discussion about this here this afternoon.

One concern I do have, and maybe Gilead and the panel can address this, is PEG-Intron, the Schering pegylated interferon is excreted by the kidney, and so is PMPA. So, the concern I have is, is that people who have HIV drug resistance, who have HVC, maybe on PMPA, maybe also starting to take peg enteron. So, I would like to have some discussion about that.

I also have no concern as some of the other community people spoke about the CD4 increase. I don't think that that is an issue.

So, in the end, I think I have raised my points that I think need to be address, and I just want to say that I do strongly support, and I think that the community, people with HIV, really need this drug for treatment-experienced people right away.

Thank you.

DR. GULICK: Thanks, Mr. Levin.

If there are no other people who wish to

speak at the open public part of this meeting--seeing none, we will go ahead and close the open public part.

I would like to turn now to Dr. Kim Struble from the FDA, who will present the charge to the committee.

Questions to the Committee

DR. STRUBLE: I am just going to go through the questions and provide some background information to help with the deliberations this afternoon.

[Slide.]

For the first question, we would like discussions on in what patient population has tenofovir demonstrated efficacy and safety, and for what indications should tenofovir be recommended.

Should it be recommended for the treatment of HIV infection, which includes both naive and treatment-experienced patients, or should it be recommended for the treatment of HIV infection in patients who have received prior antiretroviral therapy.

[Slide.]

The second question deals with the bone abnormalities. We would like to hear your

assessment today in the preclinical and clinical data with regard to bone effects. We also would like to hear if there are additional nonclinical or clinical studies that Gilead should conduct to further evaluate tenofovir-associated bone effects.

[Slide.]

This slide here has a brief summary of the nonclinical studies that are completed and are ongoing. They have completed a 42-week rat and dog study, several monkey studies ranging from 14 days to over two years in dosing, reproductive/toxicology studies, and some mechanism studies.

There is two ongoing, a two-year rat and mouse carcinogenicity studies, to also assess bone affects.

[Slide.]

With regard to the clinical data, Study 903 will provide comparative data in 601 patients for approximately 96 weeks in duration.

Bone mineral density and bone biomarkers will be available for all patients.

Also, in Study 910, which is a rollover study from Studies 901, 902, and 907, this study will provide follow up on approximately 575

patients for four years, and the bone mineral density substudies will continue over this time period. In both Studies 903 and 910, fractures will be evaluated.

[Slide.]

Regarding clinical resistance, we would like comments today on the resistance analyses that were presented by the FDA and by Gilead this morning. We would also like your recommendations for the type of clinical virology analysis that should be conducted for future antiretroviral drug development and suggestions for the type of resistance data/analyses warranting display in package inserts.

One of the issues regarding Phase IV commitments that we would like to bring up is drug interactions, because tenofovir is renally eliminated. Gilead had made a statement this morning that there were no clinically significant drug interactions, but we feel that we probably cannot definitively say that because potential interactions with other drugs that are renally eliminated have not been evaluated yet.

An interaction was seen with ddI, which is the buffered formulation, not the enteric-coated

formulation, in which there was AUC increases of 44 percent and a Cmax increase of 28 percent. No dose adjustments are being recommended, and we feel that patients should be monitored for ddI-associated adverse events if they are taking the two drugs concomitantly.

[Slide.]

So, finally, we would like your comments on the proposed second study for traditional approval, and would also like to hear comments for other study designs or patient populations that should be studied as Phase IV commitments.

Thank you.

DR. GULICK: Thanks, Dr. Struble.

Committee Discussion

DR. GULICK: Could we go back to Question No. 1. I think we want to handle each question separately. I would like to give people, everyone on the committee, an opportunity to respond to the different parts of the questions.

For Question No. 1, I think I would like to conclude our discussion actually by going around the table and having people state how they feel about the indication, but let's take the questions first and try to generate some discussion on the

very first question.

In what patient population has tenofovir demonstrated efficacy and safety? Who would like to start? Dr. Wong, thank you.

DR. WONG: I haven't talked yet today. As I read these data, the drug has been shown to be efficacious in naive patients in a short-term study and in experienced patients in both 24 and 48 week follow up, so I think it has been shown to be effective, and effective in both those populations and safe so far in both those populations.

So, the corollary is that I would recommend approval for both groups.

DR. GULICK: Dr. Yogev.

DR. YOGEV: I would put a little bit of number on this statement. I don't think it was proved to be effective, at least to my satisfaction, patient with a high viral load, who were experienced. I did a minor calculation by the data which was supplied to us.

Supposedly, 155 patient total had less than 400, which is 45 percent of the total population. We had only 15 percent out of 99 patients who had more than 5,000 or less than 400. The whole effect of this drug of being average 0.6

of viral load decrease, I would urge to think a little bit more carefully - is it really effective for patients with a high viral load.

With naive patient, I think the number are too small to make any decision, and I would like to suggest that at least I didn't see enough data for efficacy in naive. There is no question in my mind that it will show efficacy, the question will be hopefully later do we want to put it as the first choice, keeping in mind how well it might be working in the population which was tested.

DR. GULICK: Dr. Hamilton and then Dr. Pomerantz.

DR. HAMILTON: Without disagreeing with the former two speakers, I would like to add a qualification to the qualification. Whether or not naive patients have been shown to respond favorably, I think is of less concern to me at the moment, because I suspect that they will given the fact that treatment-experienced patients have, but of greater concern to me are two points.

One is that I share Dr. Yogev's view that we have not demonstrated conclusively that patients with higher viral loads, more advanced disease, equally treatment-experienced, have been shown

responsive. I believe with that caveat, that I personally would favor at the very least some serious attempts on the sponsor's part to address that question.

Of equal concern to me, however, and some of you will recognize instantly where this is coming from, is that the target population that has been principally addressed here are patients in whom I might not consider a treatment at all, given the development over the past number of years of a revised opinion about when criteria are appropriate to change or add drugs in the course of long-term management.

If a viral load is in the 4 to 10 to 15, even up to 20,000, and the CD4 is as high as it is here, very honestly, it is not an automatic for me to want to, and certainly I don't feel compelled to add something in a futile attempt, in my view, to drive the viral load to undetectable, which I think is (a) impossible in many cases, impractical in even more cases, and possibly unnecessary in all cases.

So, with those overall comments, I guess I have given my preliminary opinion here.

DR. GULICK: Dr. Pomerantz and then Dr.

Schapiro.

DR. POMERANTZ: I think this is a bit of a tough call because there is some data that is missing, and yet, most people hand-waving would suggest that they know what that data will probably turn out to be empirically.

Two issues. I think the one thing that is clear is that there isn't enough data above 50,000 in high viral loads. I think it becomes even more important when you add high viral loads in naive patients, because you don't have data there for either, and the group that I would be more concerned about are high viral loads in naive, because you have two lacking data sets there.

The second thing is that this is a different time period. There are a number of drugs in the armamentarium for naive patients, but not for many people who are in salvage therapy than the first or second, and that is where I think that modest to low viral loads, and sometimes when you have nothing else, tenofovir would be, and will be, a great drug when I would assume it will be approved. I think that has been shown reasonably well.

I think that for naive patients, there is

enough there to make them show us one more time that this actually is going to work. It is not five years ago. There are a number of drugs you can take upfront that are low pill burden, and I don't think that you need to jump the gun in those patients. I think it was nicely said by a variety of people, including our patient advocates, that it is the salvage patients that really will be able to use this, and should be there relatively quickly.

So, I would recommend its use for those who have had prior experience. I would not yet recommend its use for those who are naive, and certainly those who are naive with a high viral load.

DR. GULICK: Dr. Schapiro and then Dr. Tebas.

DR. SCHAPIRO: I would continue the thoughts of Dr. Pomerantz. I think that the question really is the risk-benefit ratio. I think, looking at the two groups, it is not if it is naive or experienced. I think in patients who do not have other options, even though there are concerns that we have not seen all the data we want to see, we haven't seen drug interactions, which I think are important, which were brought up here and

have not yet been addressed.

I think we have concern about some of the protease inhibitors, some of the dose of the protease inhibitors. We don't know what that will do. I think some of the populations that we really want to treat were not studied.

I think some of the populations, such as black women, we really don't know what the PK is happening over there. I think these concerns are risk. I think we have seen a benefit.

I think for patients who do not have many other options, the benefits do outweigh the risks, and therefore, I would strongly think that we should get this into the hands of those physician and patients right away.

The question is for patients who have many other options. Good studies are being done now, looking at if this drug is as good as others. Until we know if it is as good as the others, until we know how it does in interactions, until we know how it does in these different populations, I think the risk is greater than the benefit in patients who have many other options.

So, as opposed to, is the question naive, it is not specifically that it doesn't have

efficacy in naive, I think it will have, but I think that because there is a lot of data that is still lacking, I think if we receive that data, we would be very happy to allow it in naive patients.

I think for now the risk-benefit works out to be still somewhat worrisome, and even I think again, just a word on the community representative who got up, I think those are all excellent points, and I also think that we don't want to penalize, of course, Gilead, for doing a wonderful job and being very brave, but if we start giving to naive patients, and find out that some of these risks really end being dangerous, it will be hard to take it back.

So, I think it should be in that context.

DR. GULICK: Dr. Tebas.

DR. TEBAS: I want to concur with Jonathan Schapiro. I have lived in this country for eight years, I live in a state that the motive of the state is Show me your State, and before using this drug in naive people, I want them to show that it is as good as other combinations that we have.

I think this period of the accelerated approval is to provide drugs where there is no options, and approving it directly for naive

people, it doesn't meet those conditions, and I would wait.

Ideally, I will have the results of 903 relatively soon, and I assume as we see the data, I think it would be reasonable to approve for all HIV-infected people, even naive people, but before that, we run the risk of approving a drug that later on shows that it is inferior to current other label regimens, and we might be in a situation that it will be very awkward.

DR. GULICK: Dr. Munk.

DR. MUNK: Mr. Chairman, can I ask a question of FDA staff?

DR. GULICK: Sure.

DR. MUNK: Can FDA staff shed any light on the comment in Mr. Cheng's comments, that, in fact, prior anti-HIV agents had received the indication for which Gilead has asked based on data, for example, that may only have been generated in naive populations?

DR. STRUBLE: Yes, that is true. With the exception of Kaletra, the majority of the past approvals have been--

DR. GULICK: Can you speak up a little bit?

DR. STRUBLE: With the exception of Kaletra, the other drug development programs have been largely conducted in naive populations or patients with limited nucleoside experience. Kaletra was the first application to come forward with PI-experienced patients, that were experienced within its respective drug class. So, yes, all the other products have gotten a broad indication for the treatment of HIV infection, and that includes presumably all the spectrum of the HIV disease.

DR. MUNK: That being the case, and based on my reading of community comments, I think it sounds like it would be a departure from past practice, and, in fact, sensitive to the comments about potential risk of applying the drug to classes in which there is not yet demonstrated efficacy, it seems like we may be going in the wrong direction, that, in this case, the extension would be to naive patients, and I believe it is reasonable to assume that the risk would be less than with the case of these other drugs, where the broad indication would allow their use in experienced patients in the absence of such data.

So, I would, based on that, I would support the broader indication with the caveat that

I am not comfortable with patients with high viral loads at this point, and that that perhaps ought to be a limitation on the indication.

DR. GULICK: Dr. Kumar.

DR. KUMAR: In everything that I have reviewed both from the material given to me, as well as everything that I have heard today, as a clinician, it is clear to me that in experienced patients, that tenofovir has a very potent use.

But I also want to make a very deliberate educated leap of faith and say that there was no significant safety concerns in this treatment-experienced patients that we are most likely to see the side effects.

So, I would feel very comfortable using it for naive patients while awaiting Gilead's full presentation of its data.

I think, as a clinician, that works in the trenches, and especially in states that look at ADAP programs that will only approve for indicated approvals, to allow such a good drug to come forward and not be allowed to use in all subsets of patients will be problematic.

DR. GULICK: Dr. Stanley.

DR. STANLEY: Well, I don't necessarily

agree on that one. I think I can speak for the Texas ADAP program, since it is under my purview, and once a drug is approved and is either added to the formulary or not, we don't second guess how the physicians approve it.

I mean I have got 10,000 patients on that formula, on ADAP, and there is no way I am going to look at each and every one of those and try to second guess the physician. So, at least in Texas and, Yvette, I don't know where you got your reference earlier, but us making a limited approval would not affect its role or its availability in the ADAP program in Texas.

That being said, I continue to have concerns about making this broadly recommended, and that is, we really don't know what the best use of it is, should it be in a PI-containing regimen or does it not have to be, and that question isn't even planned to be addressed from what I can see, and I think that that is a study that I would like to see that question asked.

The proposed study is only going to look at it with an NRTI and an NNRTI. We don't know what the best way to use it upfront is, what the best combination is, and so it is clearly

efficacious in salvage therapy, and I think that we should go with that. I think it is desperate that it is available for those patients that have been on multiple drugs, but I am very nervous with now making a broad recommendation on these data.

DR. GULICK: Dr. Wood.

DR. WOOD: Just to echo some of the concerns raised by Dr. Schapiro and others, clearly, there is a need for a new antiretroviral agent that demonstrates some efficacy in treatment-experienced patients, and as Dr. Schapiro elegantly highlighted, that based on the preliminary data we have seen here, there is a greater appearance of benefit compared to risk in treatment-experienced patients. For those who are naive, the risks would appear to be greater than the benefits.

The point that I would like to raise is, if the drug is approved, it is going to be used. The FDA, state agencies are not going to regulate how practitioners and those individuals in the trenches use this drug.

Based on Dr. Hamilton's comment of the current revision in the PHS guidelines, in which much higher levels of viral loads are tolerated

before consolidation or intensification or even change in treatment therapy is recommended, the people who truly need a salvage regimen out there in the community are probably individuals with very low CD4 cell counts and viral loads greater than 50,000.

It is in that very population which is going to be rushing to seek the use of a new antiretroviral agent that we have the most limited data in.

So, I would like to again just reiterate that the sooner we can get information about the efficacy of this drug, not only in naive patients, but particularly in those individuals with viral loads of 50,000, because I think those are going to be the individuals that are clamoring for it and those are going to be the individuals, the prescribers, if the drug is licensed, are going to be prescribing it for.

DR. GULICK: Dr. Pomerantz.

DR. POMERANTZ: I just want to give a quick postscript, because I understood what Dr. Munk and my good friend, Dr. Kumar, said, and that is what I said at the beginning of my comment, which agreed with Dr. Schapiro, that it is a tough

call.

But it is important to realize that this is a dynamic field, and being here for the last four or five years, we have seen how as the armamentarium changes, your ability to make different calls change as well.

So, with naive therapy, there is enough out there for most patients to give low pill burden, most patients, low pill burden, fairly easy drug input, and it is not five years ago. I don't think we need to have two data sets missing and place it where it is not absolutely necessary right now.

I would contend that in the trenches, as was said right now by Dr. Wood, where it is absolutely necessary or in the salvage cases, and the rest, we will see when the data is there.

DR. GULICK: Dr. Wong.

DR. WONG: I guess most people disagree with me, but I just want to put another face on what we are talking about. I don't think that we, on this committee, or the FDA, should really ask sponsors when they are requesting approvals to demonstrate that the drugs that they are requesting approvals for are the best available in all

situations. I think that is not a realistic bar.

It seems to me that what is being proposed here is that Gilead be given an approval that is substantially more restrictive than the approval for really any other antiretroviral drug. I look at that in the context of their having shown us today very convincing data that their drug is efficacious in a group for which we haven't really seen these sorts of convincing data for efficacy before.

So, I really think that what they have shown is that their drug is safe and effective for adults with HIV infection, and I would not try to split that group to a greater extent than what we have done in the past.

DR. GULICK: Other comments? Dr. Englund.

DR. ENGLUND: I am concerned about licensing a drug or granting our approval to a drug for which there really isn't data, and my question is how long will it take as a new member here, a new potential member, whatever I am, how long will it take to move forward when they do get the data, because it seems to me that it is within the purview of this committee to recommend that when the data is available, that we should be able to

move quickly and responsively to it.

I mean that is one of the concerns, is how long is it going to take.

DR. GULICK: Would you like to address that, someone from the Division?

DR. STRUBLE: How long it will take for?

DR. GULICK: The question is there is a naive study in progress right now. Let's say the committee recommends that it be only approved for treatment-experienced, but then this naive study becomes available, how long before that could be reconsidered in terms of the labeling of the drug.

DR. STRUBLE: Well, I think it depends on when the study actually gets submitted to us. When the study gets submitted to us, we will decide if it's a six- or 10-month review, and then we will take an action within that time frame, but I think it all depends when the data is going to be available and submitted to us.

DR. ENGLUND: I feel strongly that we do need this as a salvage protocol and that the data they submitted is good enough to consider this absolutely for the second group, for the patients who have received prior antiretroviral therapy.

DR. GULICK: Other comments? Dr. Johnson.

DR. JOHNSON: I agree with everyone, so I will probably not get asked back.

[Laughter.]

DR. JOHNSON: I think back to five years ago, and, you know, there weren't as many options, and 3TC was approved for naive and experienced patients, and we only saw half-log reduction, and we didn't care what their viral load was, and it still did better.

Here, obviously, we have all agreed that the treatment-experienced group, there was excellent data, trying to say that because they didn't study hard in 100,000 or 50,000, I think we are splitting hairs if we start restricting for a group that is desperate for a salvage drug, and I think there should be no upper limit on that, and they can gather more data, and we are all, in practice, giving four drugs anyhow often off-label, and I won't get invited back for that either.

But with regard to the treatment-naive population, let me again ask Dr. Struble, there is no precedent for half a labeling, right, we have no other HIV drugs that got approved and then we tried to go back to our universities and say remember you can't give that to drug-naive patients. It will

happen, and I believe that I agree with Dr. Wong that I have probably seen enough to accept that I could give this to a treatment-naive person with an adequate risk-benefit ratio, with a low pill burden, with more safety monitoring, and would be happy to reconsider if something desperately jumped out, but I am not hearing that it will.

DR. GULICK: Dr. Sun and then Dr. Hamilton.

DR. SUN: I don't get to vote, so I don't have to take a position, but I would offer a few observations. I think, first, on the safety side, it seems like the evidence suggests that this is a fairly safe drug, and I think even though it was studied primarily in experienced patients, one can fairly easily make that extrapolation that it will have a similar profile in naive patients.

On the other hand, as someone pointed out, naive patients may have a different risk-benefit equation that they apply to a drug.

With regards to efficacy, again echoing many of the comments that were made, it is a lot easier to extrapolate going from experienced to naive than going the other way. So, I think there is biological plausibility for expecting that this

drug will work in naive patients.

Although naive patients will probably tend to have higher viral loads than the patients that were studied in 902 and 907, we have to remember they will also be getting more active drugs than what they received in the trials that were conducted.

The third point is I would just caution people against making too many historical comparisons, because the field has changed so much. A few years ago we didn't have treatment-experienced patients or we didn't have PI-experienced patients when the first PIs came along obviously, so I think it is a little hard to compare today with three or four years ago even.

The last thing I would point out is that I think this becomes a little bit philosophical in terms of how much direct evidence you need to support an indication, and I would point out that we already do a fair amount of extrapolating, so I think most of the labels read that drug X is approved to be used in combination with other antiretrovirals without specifying what they are, and it is generally the case that clinical trials don't test every single combination that is

available.

DR. GULICK: Dr. Hamilton.

DR. HAMILTON: Over the period of the four years that I have been on this committee, I have learned a number of things. One of them is that there are at least two potentially competing responsibilities that, as a member of the committee, I have perceived that I have.

I say potentially competing because they may be actually complementary, but the first, which I thought initially was my responsibility, was to evaluate the data and just be hard and fast, cut and dried, black and white, and while I think that is still an exceedingly important role, a second perceived responsibility, and one that I would say this is only by implication, not that anybody has ever told me this, but what we ultimately recommend as a committee, what we decide as a committee comes across to the public as a recommendation.

So, if we approve this drug, then, we in essence are recommending that everybody use it for whatever they want, and, in fact, they may do that, I don't know, they probably will, but I think it is important to separate in our own minds what it is that we are actually saying here.

I betcha we all pretty much agree very closely on what the data show here, but it seems to me ultimately, we are going to have to go beyond that and hopefully try and make some accommodation with a very cooperative sponsor in my view for satisfying these other concerns in a collegial and reasonable way without becoming too overly consumed with details.

Those are all just kind of very general comments. I don't know that they have any meaning for anybody for me, but I offer them.

DR. GULICK: Thanks.

Dr. Yogev.

DR. YOGEV: Well, it makes some sense to me, if it helps you.

[Laughter.]

DR. YOGEV: Maybe I didn't put it the first time. I am concerned about the data and the viral load also connected to the resistance that we didn't really put together, but if the viral load average median in those studies, 907, if I recall correctly, was 2,600, and 3 percent are resistant to the drug, on a virus which mutates so much and you are going to give it to the naive patient with a 50 and 100,000, are we going to see much more

resistance developing.

Keep in mind that you are also exposing a population again to a single drug that 10 percent or higher are HBV, that are not yet suffering from it, but you are helping them to become resistant before you see what the benefit is, and there are so many other drugs around.

That is why I would like to see it, at this point, restricted to the smaller viral load, when it is active, or to the experienced patient, because they are really running out of choices. But I think the resistant issue over here, the way it develops, and way it was presented, is not clear to me there was a higher load and you won't see more.

DR. STANLEY: Dr. Hamilton, your comments did ring with me and meant a lot to me, and particularly the second role that you postulated for us, where we make a recommendation, and the public hears it, and that is what concerns me in this situation again is that this is a very important drug for salvage.

It is a very important drug for that population. Once it is approved and out there, yes, the people in the trenches will use it as they

wish, and so it is not like we are truly limiting the drug, but yet what I am comfortable with, with what the science is that we have seen, is to say this is the area where we know it is efficacious is in this population, and that is where we target it.

What the individual prescriber wants to do is always up to them.

DR. GULICK: Let me try to summarize what we have been saying. In terms of what patient population, we are comfortable with safety and efficacy being demonstrated. The committee was unanimous in saying for the treatment-experienced population, that we feel quite comfortable that that has been demonstrated.

For the naive population, it was noted that there is relatively little data to go on. Several people voiced the probability that we can extrapolate from the experienced population in terms of virologic effect and safety issues to the naive population.

There was some concern about those with high baseline viral load levels, and it was noted that there is relatively little data to tell us about safety and efficacy in that particular group.

In terms of the indication, and again I

will remind people after this I want to go around and ask each person what they would suggest, we had a lot of debate, and there are differences of opinions around the table.

Dr. Pomerantz summed it up best by saying this is a tough call, and most of this revolves around how much extrapolation you are willing to do from the data in hand. To support the concerns of the people who would seek to have an indication limited to treatment-experienced population, this thought primarily centered on several points.

One was how comfortable are we that there is no data to support this indication and how willing we are to extrapolate.

Number two, people made the point that this is a different time period in the evolution of HIV drugs. There are 15 drugs approved for the treatment of disease today.

Of note, one point that wasn't made was that in the accelerated approval guidelines is the quote that "a meaningful benefit over existing treatment must be demonstrated," and there was some discussion that we really don't have comparative data between tenofovir and the other agents that one might substitute tenofovir for in naive

patients.

Dr. Schapiro brought up what is the risk-benefit ratio, and others echoed this and really said that the risk-benefit ratio in experienced patients may be quite different from those in naive patients.

People spoke about the safety issues, about drug interactions, about what are the optimal treatment regimens that you would use in each of these populations, what is the best combination of drugs.

These are questions that we simply have answers for. On the other hand, people who would support a broad indication, and several members of the committee support that point of view, really were more comfortable extrapolating data from what we know about the treatment-experienced group. People said we assume that it is okay from a safety and virologic point of view, it makes biologic plausibility that that approach would work.

There is precedence in labeling from past drugs to look at the other direction, going from naive to experienced, and doesn't it make some sense to go from experienced to naive.

People brought up concerns about the